Gallstones in a group of Iraqi patients with type 2 diabetes mellitus

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ABSTRACT

الأهداف: التعرف على نسبة مرض حصى الصفراء عند مرضى داء السكري، بالإضافة إلى التعرف على تأثير مدة الإصابة بداء السكري ونسبة HbA_{1c} على زيادة نسبة الإصابة بحصى الصفراء.

الطريقة: أُجريت هذه الدراسة في قسم الطب، مستشفى اليرموك التعليمي، بغداد، العراق وذلك خلال الفترة من أبريل إلى ديسمبر 2008م. يتناول البحث دراسة 100 مريض مصاب بداء السكري من النوع الثاني والذين تتراوح أعمارهم ما بين 30–90 عاماً. لقد تم فحص كل مريض بالأمواج فوق الصوتية لكيس الصفراء لبيان نسبة وجود حصى الصفراء عندهم وكذلك تم قياس نسبة السكر بالدم ونسبة HbA_{1c}، وتم استجواب كل مريض حول وجود حصى المرارة في العائلة. وتمت مقارنة النتائج مع مجموعة ثانية تضم 100 شخص غير مصاب بداء السكري لهم نفس خصائص المجموعة الأولى من حيث الجنس والوزن والعمر، وأُجريت لهم نفس الفحوصات والنماذج المختبرية. لقد تم تقسيم المجموعة الأولى إلى قسمين وذلك حسب نتائج فحوصات الموجات فوق الصوتية. تضم المجموعة الأولى المرضى الذين لديهم حصى الصفراء، وتضم المجموعة الثانية المرضى الذين لم تكشف الفحوصات عن إصابتهم بحصى الصفراء. وتمت المقارنة بين المجموعتين من حيث تأثير مدة الإصابة بداء السكري ونسبة HbA_{1c} على معدل إصابتهم بحصى الصفراء.

النتائج: لقد تم التوصل من خلال هذه الدراسة إلى الآتي: وُجد أن مرض حصى الصفراء أكثر نسبة في مرضى داء السكري بحوالي النصف (33%) بالمقارنة مع نسبة 17% فقط في الأشخاص الغير مصابين بداء السكري. ولم يوجد اختلاف في نسبة مرض حصى الصفراء في مرضى داء السكري والأشخاص الأصحاء مع زيادة عمر المريض أو وجود حصى الصفراء في أحد أفراد العائلة. لقد كانت نسبة الزيادة بالإصابة بحصى الصفراء أكثر في النساء المصابات بداء السكري وخصوصا اللاتي حملن لأكثر من ثلاث مرات منه في باقي النساء الصحيحات واللاتي لهن نفس العدد من الحمل. وكانت نسبة الزيادة بالإصابة بحصى الصفراء تزيد في مرضى داء السكري بزيادة الوزن أو عندما يكون مؤشر كتلة الجسم أكثر من 25 كغم\متر^2، ولكن لا يوجد اختلاف في المرضى قليلي الوزن. وهنالك زيادة ملحوظة في نسبة مرضى داء السكري المصابين بحصى الصفراء مع زيادة مدة الداء أو ارتفاع نسبة HbA_{1c} في الدم.

خاتمة: أظهرت الدراسة بأنه يُفضل الاستقصاء عن أمراض حصى الصفراء في مرضى داء السكري خصوصاً أولئك الذين يعانون منه لفترة طويلة والذين كانت نتائج تحليل HbA_{1c} لديهم عالية، بالإضافة إلى الإناث وخصوصا اللاتي حملن لأكثر من ثلاث مرات.

Objectives: To find the frequency of gallstones in diabetic patients, and to study the relationship between the frequency of gallstones and state of control, and duration of diabetes mellitus (DM).

Methods: This case control study was carried out in the Department of Medicine, Al-Yarmook Teaching Hospital, Baghdad, Iraq from April 2008 to December 2008. We enrolled 100 patients with type 2 DM (60 females and 40 males) as a test group and 100 subjects with no DM (61 females and 39 males) as a control group. Both groups were comparable for gender, age, and body mass index (BMI) and examined by ultrasound to find the gallstones. Blood samples were taken for fasting blood glucose and the BMI was measured. Both groups were asked regarding age, gender, family history of gallstones, and parity for females. The tested groups were further divided into 2 subgroups: with gallstone and without gallstone. The association between duration of DM and hemoglobin A1c level with gallstone were assessed.

Results: Gallstones were found in 33% of diabetic and 17% of non-diabetic patients. There was no significant difference in age and family history of gallstone between diabetic and non-diabetic groups. However, gallstones was higher in diabetic patients with BMI >25Kg/m^2, with increased duration of DM, with increased HbA1C, and multiparous females.

Conclusion: The frequency of gallstones in type 2 DM increases in obese patients, females with increased parity, increased level of HbA1c, and is positively correlated with the duration of DM.

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Gallstones are collections of solid material that form inside the gallbladder, if there is a change or imbalance in the composition of bile, such as too much cholesterol, increased amounts of pigment material, and/or reduced levels of bile acids.[1] Gallstones may also result from impaired gallbladder contraction, which would lead to incomplete emptying of the gallbladder in response to a fatty meal.[2] There is a marked variation in overall gallstone prevalence between different ethnic populations.[3] Generally, there appears to be higher rates of cholelithiasis in western Caucasian, Hispanic, and Native American populations and lower rates in eastern European, African American, and Japanese populations.[4] The worldwide prevalence of diabetes mellitus has risen dramatically over the past 2 decades, from an estimated 30 million cases in 1985 to 177 million in 2000.[5] The prevalence of type 2 diabetes mellitus (T2DM) is rising more rapidly because of increasing obesity and reduced activity levels as countries became more industrialized.[6] In many studies, it has been emphasized that the reduced motility of diabetic patient's gallbladder may be an important factor causing the stones formation,[7] particularly, it is explained that the reduced motility of gallbladder in diabetes can be caused by an abnormal autonomic nervous system and gastrointestinal hormone,[8] and stasis per se may lower the cholesterol saturation index but its detrimental effect on gallbladder locally, and thus, accelerates cholesterol crystal formation.[9] Type 2 diabetes is usually found in obese subjects, and it is a well-documented fact that obesity is a risk factor for gallstones particularly among women;[10,11] therefore, the association of gallstones with altered carbohydrate metabolism may be hypothesized.[12] In addition, other risk factors such as aging are common to both diseases;[13] therefore, we designed a case control study to determine the prevalence of gallstones in a group of patients with T2DM, and in control group without diabetes depending on ultrasonographic study of both groups. The present study was to determine the prevalence of gallstone in patients with T2DM, to study the relationship between the prevalence of gallstone and the state of glycemic control among diabetic patients, and the duration of their T2DM.

Methods. This study was carried out in the Medical Department, Al-Yarmook Teaching Hospital, Bagdad, Iraq from April 2008 to December 2008.

One hundred patients with T2DM were included in this study (after obtaining their consent) as a test group, 60 females and 40 males, and the average of ages were 57±20 years, and 100 non-diabetic patients as a control group consist of 61 females and 39 males with an average age of 52±32 years.

Inclusion and exclusion criteria. All subjects in the test group was fulfilled the WHO criteria in diabetes mellitus.[14] The subjects with diabetes onset prior to the age of 30 or treated initially by insulin or with history of diabetic ketoacidosis were considered as type 1 diabetes mellitus and excluded from the study. Diabetic patients were asked about the date of their diagnosis and duration of disease. Blood samples were drained to determined the hemoglobin A1c (HbA1c) level and any patient with hemoglobinopathy by history or available blood picture were excluded from the study. The control group included individual who did not have history of diabetes mellitus and any symptom or sign of diabetes mellitus and blood samples were taken for measurement of fasting blood sugar and any persons with fasting plasma glucose >126 mg/dl was excluded from the study.

Individuals in both groups were asked about the family history of gallstone and the female were asked about the number of pregnancies. The body mass index (BMI) was calculated by dividing the weight in kilograms by height (m^2). Blood samples were taken in the morning after a 12-hour fast. Gallbladder ultrasonography was performed by trained operator unaware of the subject history. Gallstone defined as mobile echoes in gallbladder lumen. The final gallbladder status was recorded as follows: normal at ultrasonography, presence of gallstones at ultrasonography, presence of biliary sludge at ultrasonography, and previous cholecystectomy.

This study was conducted in 2 phases. In the first phase, we compared case and control group to determine the prevalence of gallbladder disease in patients with T2DM (case) in comparison with individuals without diabetes (control), both groups were matched for age, gender, and BMI. The second phase was a comparison study within diabetic subjects to determine the effect of duration of diabetes, level of fasting blood glucose, and level of HbA1c on prevalence of gallstone.

Statistical analysis. The statistical significance of an association between 2 variables was assessed by Chi-square (x^2) test of independence. An estimated p value is considered statistically significant if it is <0.05.

Results. **Table 1** shows the prevalence of gallbladder disease in diabetic and non-diabetic subjects. We observed that it was more frequent in non-diabetic subjects ($p<0.01$).

The prevalence of gallbladder disease was significantly associated with age and the prevalence increased as age increase both in diabetic and non-diabetic subjects. There were mild differences between the 2 groups, but no statistically significant difference ($p>0.05$) (**Table 2**).

The prevalence increased with increasing BMI both in diabetic and non-diabetic subjects (**Table 2**). There was no significant difference in prevalence of gallbladder between the 2 groups when BMI was <25 kg/m^2 (13.3% versus 16.7%, $p>0.1$). But the prevalence increased in diabetic subjects when BMI was ≥25 kg/m^2 compared with non-diabetic subjects (32.7% versus 14.9%, $p<0.05$). Frequency of gallbladder in both diabetic and non-diabetic. Subject with positive family history of gallbladder was higher compared with subjects without family history of gallbladder, but there was no statistical significant difference between diabetic and non-diabetic subjects ($p>0.05$) (**Table 2**).

Table 3 shows the prevalence of gallbladder in diabetic patients increased significantly in association with female gender (40% in diabetic versus 13.1% in non-diabetic subjects, $p<0.01$) in comparison to that of males (22.5% in diabetic versus 23.1% in non-diabetic subjects, $p>0.05$). The prevalence increased with increasing number of pregnant women in both diabetic and non-diabetic subjects (36.8% and 12.5% in women with parity and ≤3 to 41.5% and 13.3% in women with parity >3). There is a mild difference between the 2 groups, but statistically significant, only when parity was >3 ($p<0.05$) (**Table 3**).

Table 4 shows the prevalence of gallstone according to the duration of diabetes (in years). The prevalence of gallbladder increased when the duration of diabetes increased from <5 years to 5-10 years and >10 years ($p<0.05$).

The prevalence of gallstone increased from 0% in diabetic patients with HbA1c level <6 to 12.5% at HbA1c level of 7-7.9. The HbA1c level is strongly associated with increased risk of gallbladder in diabetic subjects ($p<0.03$) (**Table 5**).

Table 1 - The prevalence of gallstone in diabetic and non-diabetic subjects.

Group	Subjects with gallstones		*P*-value
	n	(%)	
Diabetic (n=100)	33	(33)	<0.01
Non-diabetic (n=100)	17	(17)	

Table 2 - The relation between gallstone (GS) and age, body mass index, and family history in diabetic and non diabetic subjects.

Variables	Diabetic			Non-diabetic			*P*-value
	N	Patients with GS n (%)		N	Subjects with GS n (%)		
Age groups (years)							>0.05
30-39	11	1	(9.1)	21	1	(4.8)	
40-49	13	3	(23.1)	20	4	(20.0)	
50-59	27	7	(25.9)	25	3	(12.0)	
60-69	28	10	(35.7)	11	3	(27.3)	
70-79	15	8	(53.3)	17	3	(17.6)	
80-89	6	4	(66.7)	6	3	(50.0)	
Body mass index							
<20	5	0	(0)	6	1	(16.7)	>0.1*
20-24.9	15	2	(13.3)	18	3	(16.7)	>0.1*
25-29.9	49	16	(32.7)	47	7	(14.9)	<0.05*
≥30	31	15	(48.4)	29	6	(20.7)	<0.03*
Family history							
Positive	22	14	(63.9)	14	5	(35.7)	>0.06†
Negative	78	19	(24.4)	86	12	(14.0)	> 0.1†

*$p<0.05$, †$p>0.05$

Table 3 - The relation between gallstones and gender and parity in diabetic and non-diabetic subjects.

Variables	Diabetic			Non-diabetic			*P*-value
	N	With gallstone n (%)		N	With gallstone n (%)		
Gender							
Female	60	24	(40.0)	61	8	(13.1)	<0.01*
Male	40	9	(22.5)	39	9	(23.1)	>0.05*
Parity							
≤3	19	7	(36.8)	16	2	(12.5)	>0.05†
>3	41	17	(41.5)	45	6	(13.3)	<0.05†

*p>0.05, †p>0.05

Table 4 - The relation between the duration of type 2 diabetes mellitus and gallstones (GS) in diabetic patients (N=100).

Duration of diabetes (years)	N	Diabetic with GS n (%)		*P*-value
<5	21	3	(14.3)	<0.05
5-10	39	12	(30.8)	
>10	40	18	(45.0)	

Table 5 - The relation between hemoglobin A1c (HbA1c) and gallstone (GS) in diabetic patients (N=100).

Variables	N	Diabetic with GS		Diabetic without GS		*P*-value
		n	(%)	n	(%)	
HbA_{1c}						<0.01
<6	9	0	(0.0)	9	(100)	
6-6.9	19	7	(36.8)	12	(63.2)	
7-7.9	16	2	(12.5)	14	(87.5)	
8-8.9	25	9	(36.0)	16	(64.0)	
9-9.9	16	5	(31.3)	11	(68.8)	
>10	15	10	(66.7)	5	(33.3)	
		p<0.03				

Discussion. The frequency of gallstone in diabetic patients (33%) and control (17%) groups were in agreement with Hahm et al[14] study. It showed that there was a higher prevalence of gallstone in diabetics (32.7%) compared to controls (20.8%).[14]

The pathophysiological basis of increased prevalence of gallstone in diabetes mellitus is uncertain.[15] Factors were suggested to be associated with increased gallstone prevalence in diabetic patients included supersaturation of bile,[16] changes in the cholesterol nucleation,[6] and decrease motility of gall bladder.[17] One study suggested that diabetic subjects secrete more lithogenic bile than non-diabetic subjects.[18] Another study documents that the gallbladder volume in diabetics was significantly higher compared with that of control; moreover, in the case diabetic with autonomic neuropathy, gallbladder motility was markedly reduced in comparison with diabetic without autonomic neuropathy. Impairment of gallbladder motility complicated with autonomic neuropathy causes stasis and result in cholesterol gallstone crystal formation and gallstones growth.[19]

Our study shows that the age and family history continue to be the risk factors for gallstone[17] even among diabetic patients with no significant differences between the 2 groups. This can be explained by increasing age causes increased biliary secretion of cholesterol, decreased size of bile acid pool, decreased secretion of bile salts.[8] However, diabetic female and diabetic obese patients with more than 25 kg/m^2 shows increased in frequency of gallstone in comparison with non-diabetic subjects. Obesity is associated with increased insulin resistance and hyperlipidemia, and positive association was reported between gallstone and high insulin level. Gallstone may be the result of higher insulin concentration observed in obese diabetic patients compared to that of non-diabetic obese subjects. Similar results had been reported in previous studies.[20] Our study was comparable with previous case control study of clinical gallbladder disease in T2DM patients.[21] Steven et al,[19] found that the female gender increased the risk of gallstone more in diabetic patients than in non-diabetic subjects. This may be because estrogens

stimulate hepatic lipoprotein receptors, increase uptake of dietary cholesterol, and increase biliary cholesterol secretion, also natural estrogens, other estrogens, and oral contraceptives lead to decreased bile salt secretion and decreased conversion of cholesterol to cholesteryl esters.[8]

This study shows that the duration of diabetes was positively related to the prevalence of gallstone. The relationship between duration of diabetes and gallstone in the individuals with T2DM had been compared in 2 previous studies,[21,22] and no association found. This association could be the result of increased insulin resistance with longer duration of diabetes,[20] or increased risk of autonomic neuropathy with longer duration of diabetes.[21] Finally, there is a positive relation between gallstone and increase HbA1c level which indicate a poor glycemic control.[8] This result were in agreement with a previously published study,[22] which showed that gallstone formation was significantly greater in diabetic with high HbA1c level in comparison with control. Blood glucose concentration affect gallbladder motility, that an acute hyperglycemia reduce the gallbladder responsiveness to CCK-33 in a dose dependant manner and that hyperglycemia reduce basal and CCK-33 stimulated plasma PP concentrations, suggesting impaired cholinergic activity during hyperglycemia.[22]

The limitation of the study is that the studied group was small in number. Future studies may be needed for correlating gallbladder function in diabetic patients and relation of gallbladder diseases, and other diabetic complications.

In conclusions, the frequency of gallstone increases with T2DM with increased duration of diabetes mellitus and high HbA1c level. There were no significant differences in age and family history. There is an increase in frequency of gallstone in diabetic obese patients and diabetic multiparuos female.

References

1. Méndez-Sánchez N, Chavez-Tapia NC, Uribe M. The role of dietary fats in the pathogenesis of gallstones. ***Front Biosci*** 2003; 8: e420-e427.
2. Bartoli E, Capron JP. [Epidemiology and natural history of cholelithiasis]. ***Rev Prat*** 2000; 50: 2112-2116. French
3. Zahor A, Sternby NH, Kagan A, Uemura K, Vanecek R, Vichert AM. Frequency of cholelithiasis in Prague and Malmö. An autopsy study. ***Scand J Gastroenterol*** 1974; 9: 3-7.
4. Greenberger NJ, Paumgartner G. Diseases of the gallbladder and bile ducts. In: Fauci A, Braunwald E, Kasper D, Hauser S, Longdo D, Jameson J, et al, editors. Harrison's Principles of Internal Medicine. 17th ed. Australia and New Zealand: McGraw Hill; 2008. p. 1991-2017.
5. Hayes PC, Simpson KJ, Garden OJ. Liver and biliary tract disease. In: Hasle HC, Chilvers ER, Boon NA, Colledge NR, editors. Davidsons Principles & Practice of Medicine. 19th ed. London (UK): Churchill Living Stone; 2002. p. 831-888.
6. Afdhal NH, Smith BF. Cholesterol crystal nucleation: a decade-long search for the missing link in gallstone pathogenesis. ***Hepatology*** 1990; 11: 699-702.
7. Afdhal NA. Diseases of the gallbladder and bile ducts. In: Golden L, Bennett S. Cecil Textbook of Medicine. 23rd ed. Philadelphia (PA): Saunders; 2007. p. 821-831.
8. Greenberger NJ, Paumgartner G. Diseases of the Gallbladder and Bile Ducts. In: Fauci A, Braunwald E, Kasper D, Hauser S, Longdo D, Jameson J, et al, editors. Harrison's Principles of Internal Medicine. 17th ed. Australia and New Zealand: McGraw Hill; 2008, p. 1991-2017.
9. Gilat T, Feldman C, Halpern Z, Dan M, Bar-Meir S. An increased familial frequency of gallstones. ***Gastroenterology*** 1983; 84: 242-246.
10. Scragg RK, McMichael AJ, Baghurst PA. Diet, alcohol, and relative weight in gall stone disease: a case control study. ***Br Med J (Clin Res Ed)*** 1984; 288: 1113-1119.
11. Shiffman ML, Kaplan GD, Brinkman-Kaplan V, Vickers FF. Prophylaxis against gallstone formation with ursodeoxycholic acid in patients participating in a very-low-calorie diet program. ***Ann Intern Med*** 1995; 122: 899-905.
12. Thijs C, Knipschild P, Brombacher P. Serum lipids and gallstones: a case control study. ***Gastroenterology*** 1990; 99: 843-849.
13. Powers A. Diabetes mellitus. In: Fauci A, Braunwald E, Kasper D, Hauser S, Longdo D, Jameson J, et al, editors. Harrison's Principles of Internal Medicine. 17th ed. Columbus (OH): The McGraw-Hill Companies; 2008. p. 2275-2304.
14. Hahm JS, Park JY, Park KG, Ahn YH, Lee MH, Park KN. Gallbladder motility in diabetes mellitus using real time ultrasonography. ***Am J Gastroenterol*** 1996; 91: 2391-2394.
15. Xu QW, Mantle M, Pauletzki JG, Shaffer EA. Sustained gallbladder stasis promotes cholesterol gallstone formation in the ground squirrel. ***Hepatology*** 1997; 26: 831-836.
16. Barbara L, Sama C, Morselli Labate AM, Taroni F, Rusticali AG, Festi D, et al. A ten year incidence of gallstone disease: The Sirmione study. ***J Hepatol*** 2002; 18 (Suppl 1): S43.
17. Chapman BA, Wilson IR, Frampton CM, Chisholm RJ, Stewart NR, Eagar GM, et al. Prevalence of gallbladder disease in diabetes mellitus. ***Dig Dis Sci*** 1996; 41: 2222-2228.
18. Laakso M, Suhonen M, Julkunen R, Pyörälä K. Plasma insulin, serum lipids and lipoproteins in gall stone disease in non-insulin dependent diabetic subjects: a case control study. ***Gut*** 1990; 31: 344-347.

19. Stone BG, Gavaler JS, Belle SH, Shreiner DP, Peleman RR, Sarva RP, et al. Impairment of gallbladder emptying in diabetes mellitus. ***Gastroenterology*** 1988; 95: 170-176.
20. Misciagna G, Guerra V, Di Leo A, Correale M, Trevisan M. Insulin and gall stones: a population case control study in southern Italy. ***Gut*** 2000; 47: 144-147.
21. de Boer SY, Masclee AA, Jebbink MC, Schipper J, Lemkes HH, Jansen JB, et al. Effect of acute hyperglycaemia on gall bladder contraction induced by cholecystokinin in humans. ***Gut*** 1993; 34: 1128-1132.
22. MacGregor IL, Deveney C, Way LW, Meyer JH. The effect of acute hyperglycemia on meal-stimulated gastric, biliary, and pancreatic secretion, and serum gastrin. ***Gastroenterology*** 1976; 70: 197-202.

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Al-Qahtani HH, Alam MK, Al-Akeely MH, Al-Salamah SM. Cholecystectomy without intraoperative cholangiogram in gallstone pancreatitis. ***Saudi Med J*** 2011; 32: 714-717.

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Youming D, Bin W, Weixing W, Binghua W, Ruoyu L, Bangchang C. The effect of h(1) calponin expression on gallstone formation in pregnancy. ***Saudi Med J*** 2006; 27: 1661-1666.